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(54) Title: NOVEL AMINO ACID DERIVATIVES (57) Abstract The use of amino acids for increasing the uptake of drugs in medicine.		

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NOVEL AMINO ACID DERIVATIVES

Field of the invention

5 The present invention relates to the use in therapy of amino acid moieties covalently coupled to drugs which are not α -amino acids or peptides and which contain a carboxylic group thereby forming prodrugs for the parent drugs. Possibly the amino acid moieties function as uptake enhancers in the intestine of mammals including man.

10

The present invention also relates to novel amino acid derivatives of pharmaceutically active compounds which are not α -amino acids or peptides and which contain a carboxyl group as prodrugs in pharmaceutical compositions. In particular the present invention relates to derivatives of phosphonoformic acid (PFA) and the use thereof as prodrugs in pharmaceutical compositions. The PFA derivatives can be formulated for oral administration resulting in high

15 bioavailability as measured by the level of PFA in the blood upon ingestion.

20

The present invention also relates to processes for the preparation of the PFA derivatives.

25

The present invention also relates to a method of improving the transport of pharmaceutically active compounds which are not α -amino acids or peptides and which contain a carboxyl group via the intestinal mucosa into the blood of mammals. The improved transport is accomplished by chemical modification of the parent drug with a bioreversible drug moiety which is disclosed in the present invention and which mediates the active uptake of the parent drug. PFA is a parent drug which is particularly suitable for improved transport according to this method.

30

The present invention also relates to a method for the therapeutic and prophylactic

control and treatment of viral infections in humans. These include infections caused by all human herpesviruses, including cytomegalovirus (CMV), herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), Epstein-Barr virus (EBV), varicella zoster virus (VZV), human herpesvirus 6 (HHV-6) as well as by human
5 immunodeficiency virus (HIV).

Definitions

The following abbreviations and definitions will be used hereinafter.
10

The abbreviation "i.v." stands for "intravenous".

The abbreviation "p.o." stands for "peroral".

15 The abbreviation "PFA" stands for "phosphonoformic acid".

The abbreviation "DEPFA" stands for "di-(O-ethyl)phosphonoformic acid".

The abbreviation "DEPF-Gly" stands for the derivative of DEPFA with glycine.
20

The term "foscarnet" is defined herein as foscarnet sodium, the hexahydrate of the trisodium salt of phosphonoformic acid.

The term "bioavailability" is defined herein as the fraction of an oral dose that
25 reaches the systemic circulation.

The term " C_{\max} " is defined herein as the peak or highest drug concentration in the systemic circulation.

30 The term "AUC" is defined herein as the total integrated area under the

concentration/time curve. It is an estimate of the amount of drug absorbed.

The term "CMV end-organ disease" is defined herein as the disease associated with any organ infected by cytomegalovirus.

5

"F_{abs}" is the fraction of the drug absorbed which enters into the blood, i.e. $AUC_{oral}/AUC_{i.v.}$.

Background of the Invention

10

Intravenous formulations of PFA are well known and are disclosed in U.S. Patent Nos. 4,215,113; 4,339,445; 4,665,062 and 4,771,041.

15

PFA inhibits replication of all known herpesviruses in vitro including cytomegalovirus (CMV), herpes simplex virus types 1 and 2 (HSV-1, HSV-2), human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV) and varicella-zoster virus (VZV) as well as certain retroviruses including the Human Immunodeficiency Virus (HIV).

20

Treatment of CMV infections in AIDS patients and patients infected with herpesvirus with foscarnet is at present by intravenous injections. This mode of treatment is burdensome where foscarnet must be administered daily. The development of an oral formulation is therefore very desirable since it would offer a much more convenient method of treatment and thus result in easier, more reliable compliance. While oral formulations of PFA have been tested there is no known proven effective composition available on the market to date.

25

The oral administration of an aqueous solution of intravenous foscarnet in animals leads to reduced and inconsistent absorption from the gastrointestinal tract (GI tract) and therefore, low bioavailabilities and low peak blood levels, e.g. in the dog

30

(Ritschel et al., 1985, Meth. and Exptl. Clin. Pharmacol. 2:41-48).

One explanation of the low bioavailability might be that PFA is absorbed poorly in the GI tract because of its being charged at the pH of the GI tract.

5

Another explanation of the low bioavailability might be that PFA is rapidly degraded in the stomach by the inherent low pH as the drug is acid labile. This acid lability may at least in part account for the lower amount of PFA available for absorption, and therefore, the low bioavailabilities previously attained. The studies
10 of Ritschel et al. (1985) showed that the absorption of PFA in an animal having a stomach pH close to neutral (the rabbit), is much better than in one with an acidic stomach pH (the dog), thus resulting in a higher bioavailability. Bunsgaard et al. (Int. J. of Pharmaceutics, 63, 1990, 213-218) studied the decarboxylation of foscarnet in acidic solution and concluded that intragastric degradation may be of
15 significance for the absorption of foscarnet upon peroral administration.

All attempts in the past to administer oral foscarnet to human subjects using the currently approved intravenous formulation have been suboptimal and thus, unsuccessful. (Sjövall et al., 1988, Clin. Pharm. Ther., 44:65-73 and Barditch-
20 Croyo et al. 1991 7th Intl. Conf. on AIDS, Florence, Italy).

Alkyl derivatives of PFA are known from EP 0 003 007 as are the antiviral effects in vitro and in vivo in animals of such compounds and of pharmaceutical compositions thereof. So far, however, no drug based on any of these substances
25 has become available neither in oral nor in any other formulation.

Amide derivatives of PFA are known from EP 0 003 008 as are the antiviral effects in vitro and in vivo in animals of such compounds and of pharmaceutical compositions thereof. So far, however, no drug based on any of these substances
30 has become available neither in oral nor in any other formulation.

Prodrugs of phosphorus derivatives which are designed for penetrating the blood brain barrier have been described in Eur. pat. appl. No. 91912398.4 (Glazier, A.).

5 An objective of the present invention is to provide novel derivatives of PFA suitable for oral formulation which can be administered to humans and can deliver high concentrations of PFA into the blood of patients.

10 Another objective of the present invention relates to the use of a chemical modification of PFA to be delivered via the intestinal mucosa into the blood as a means of improving the uptake of PFA.

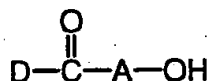
15 It is a further objective of the present invention to provide formulations of derivatives of PFA which exhibit acceptable absorption rates, and high and effective bioavailability.

Another objective of the present invention relates to the use of an effective amount of flavoring agent to provide the level of flavor desired to mask the taste of the oral formulations of prodrugs of PFA.

20 Summary of the Invention

In a general aspect the invention comprises a compound of the formula

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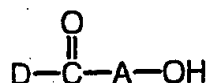
wherein



is a radical of a pharmaceutically active compound D-COOH,

which is not an α -amino acid or peptide, and which is able to form an amide bond with the N-terminal group of an amino acid residue A as defined below.

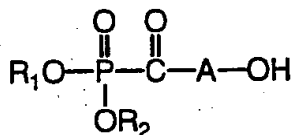
5 The invention also comprises a pharmaceutical composition containing a compound of the general formula



10 as an active ingredient and the use of such compositions of the compounds in the therapy of the diseases which are appropriate for treatment by the pharmaceutically active compound.

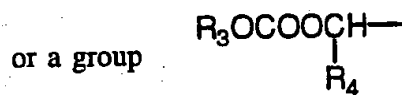
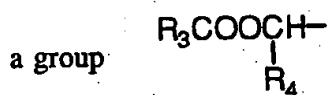
15 The present invention results from the following unexpected finding: An amino acid derivative of di-(O-ethyl)phosphonoformic formulated and administered in aqueous saline solution to rats is taken up effectively and bioconverted to release high levels of PFA into the blood.

20 The amino acid derivatives of the present invention have the general formula I:



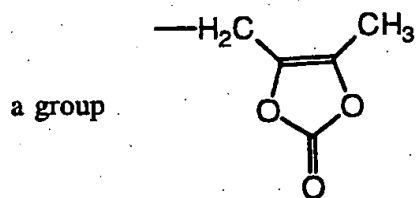
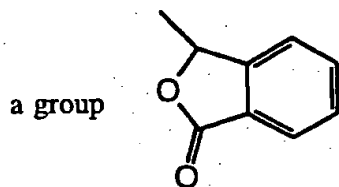
25

wherein R_1 and R_2 each independently are hydrogen; a branched or unbranched C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl or C_{1-6} -alkoxy- C_{1-6} -alkyl group which is optionally substituted with hydroxy, amino, halogen or oxo; a benzyl group;

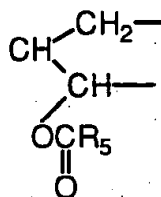


wherein R_3 is a branched or unbranched C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl or C_{1-6} -alkoxy- C_{1-6} -alkyl group which is optionally substituted with hydroxy, amino, halogen or oxo; and R_4 is

5 hydrogen or a C_{1-4} -alkyl group;



or wherein R_1 and R_2 together form a group



5

wherein R_5 is a branched or unbranched C_{1-6} -alkyl or C_{1-6} -alkoxy group;

A is an amino acid residue which is selected from glycyl, alanyl, valyl, norvalyl, leucyl, isoleucyl, norleucyl, phenylalanyl, tyrosyl, seryl, homoseryl, threonyl, cysteinyl, methionyl, tryptophyl, α -aspartyl, α -glutamyl, arginyl, lysyl, histidyl, ornithyl, prolyl or 4-hydroxyprolyl, either in the L- or in the D-configuration; or physiologically acceptable salts thereof.

The derivatives of PFA of the present invention are effective for the treatment of HIV infections and human herpesvirus infections by inhibiting the replication of the human immunodeficiency virus (HIV-1 and HIV-2), cytomegalovirus (CMV), herpes simplex virus types 1 and 2, (HSV-1 and HSV-2), Epstein-Barr virus (EBV), varicella zoster virus (VZV) and human herpesvirus 6 (HHV-6).

20

Detailed description of the invention

The present invention provides compounds which are the amino acid derivatives of pharmaceutically active compounds which are not α -amino acids or peptides and which contain a carboxyl group which can form an amide bond to an amino acid. Most preferred are derivatives of such drug molecules with glycine, L-alanine, L-proline, L-4-hydroxyproline, L-phenylalanine and L-tyrosine. In particular the present invention relates to novel derivatives of PFA in which an amino acid is attached to the carboxyl group of PFA by means of an amide bond.

30

The present invention also provides a method of enhancing the uptake of PFA and derivatives thereof into the blood by coupling an amino acid via an amide bond thereto.

5 The present invention also provides:

A. A method for treatment of diseases caused by viruses in animals including man, comprising administering to an animal so infected a therapeutically effective amount of a compound of the formula I or a physiologically acceptable salt thereof.

10

B. A method for the treatment of diseases caused by viruses in animals including man, by inhibiting the activity of viral polymerase, characterized by administering to an animal so infected a compound of the formula I or a physiologically acceptable salt thereof in an amount effective for inhibiting the activity of said viral polymerase.

15

C. A method for inhibiting the activity of reverse transcriptases of viruses in animals including man, by administration to an animal a compound of the formula I or a physiologically acceptable salt thereof in an amount sufficient for inhibiting the activity of said reverse transcriptase. Particular reverse transcriptases are the reverse transcriptases of retroviruses, such as visna, sarcoma and leucemia viruses, and human immunodeficiency virus (HIV).

20

D. A method for inhibiting the multiplication of virus, in particular herpesviruses, influenza virus and hepatitis B virus, and retroviruses in animals including man, by administering to an animal in need of such treatment a compound of the formula I or a physiologically acceptable salt thereof in an amount sufficient for inhibiting said multiplication.

25

30 E. A method for inhibiting the growth of virus-transformed cells in animals

including man, characterized by administering to an animal in need of such treatment a compound of the formula I or a physiologically acceptable salt thereof in an amount sufficient for inhibiting said growth.

5 The invention also relates to the use of a compound of the formula I or a physiologically acceptable salt thereof, in each of the above given methods A, B, C, D and E. For example, the invention relates to the use of a compound of the formula I or a physiologically acceptable salt thereof, for

10 a) inhibiting the replication of virus in animals including man, in particular herpesvirus, influenza virus, hepatitis B viruses and human immunodeficiency virus.

b) for inhibiting the growth of virus-transformed cells in animals including man.

15

Furthermore, the invention provides pharmaceutical preparations comprising as active ingredient a compound of the formula I or a physiologically acceptable salt thereof, optionally in association with a pharmaceutically acceptable carrier. The invention also encompasses a process for the preparation of a medicine having
20 antiviral activity, characterized in that a compound of the formula I or a physiologically acceptable salt thereof is brought into an administration form suitable for therapeutical purposes, and the shaped medicine obtained by such process.

25 In the present context, the terms "C₁₋₄-alkyl" and "C₁₋₆-alkyl" as a separate group or as part of a group designates alkyl groups with 1-4 or 1-6 carbon atoms which may be straight or branched such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl etc. The term "C₂₋₆-alkenyl" designates mono-unsaturated alkyl groups with 2-6 carbon atoms which may be straight or branched,
30 preferably straight, in which the double bond may be present anywhere in the

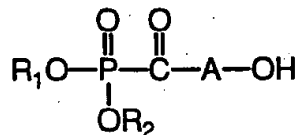
chain, for example vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl etc. The term "C₂₋₆-alkynyl" designates an alkyl group with 2-6 carbon atoms and incorporating a triple bond, e.g. ethynyl, 1-propynyl, 2-propynyl, 2-butyne, etc. The term "C₃₋₈-cycloalkyl" as a group or as part of a group designates a cyclic alkyl group with 3-8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. The term "C₁₋₆-alkoxy" designates groups comprising an oxa function substituted with an alkyl group as defined above. The term "C₃₋₈-cycloalkoxy" designates groups comprising an oxa function substituted with a cycloalkyl group as defined above. The term "halogen" designates Cl, Br, I and F.

Preferred groups of the radicals R₁ and R₂ in the formula I below are ethyl, propyl, isopropyl, acetoxymethyl, acetoxyethyl, pivaloyloxymethyl, 1-(ethoxycarbonyloxy)ethyl, phthalidyl and (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl. Preferred amino acid residues A are glycyl, L-alanyl, L-phenylalanyl, L-tyrosyl, L-prolyl or L-4-hydroxyprolyl.

Preparation

Reference to "meaning given above" for R₁, R₂ and A as used below refers to the definitions given in formula I.

Compounds of the general formula I



wherein R_1 , R_2 and A are as defined above are prepared by known methods for the synthesis of carbamoylphosphonates, for example as described by T. Reetz et al in J. Am. Chem. Soc. 77 (1955) 3813 and in Houben-Weyl, Methoden der Organische Chemie, Auflage 4, Band XII/1, Organische Phosphorverbindungen, p. 453-458. Examples of such methods are the following.

A. Reacting a compound of the formula II



wherein R_1 and R_2 have the meaning given above and R_7 is an aliphatic cycloaliphatic, araliphatic, aromatic or heterocyclic leaving group, such as C_{1-6} -alkoxy, C_{3-8} -cycloalkoxy, benzyloxy, phenoxy, 4-nitrophenoxy, imidazolyl or succinimidoxyl with an amino acid derivative H-A-OR_6 , wherein A has the meaning given above and R_6 is a suitable protecting group such as methyl, ethyl or benzyl, followed by removal of the protecting group R_6 to give a compound of the formula I.

Preferentially the carbamoylphosphonate-forming reaction is performed in a solvent, such as for example ethanol or dimethylformamide, at a temperature from 0°C to 100°C for 1 hour to 5 days.

25

The protecting group R_6 may be removed by hydrolysis with a base such as, for example, 0.5M - 2M sodium hydroxide, lithium hydroxide or potassium hydroxide in water, methanol, ethanol or aqueous tetrahydrofuran. The protecting group R_6 may also be removed by enzymatic hydrolysis, for example with porcine liver esterase. Examples of such methods are described, for example, by H. G. Davies et

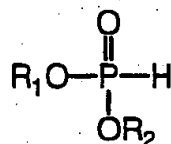
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al in Best Synthetic Methods; Biotransformations in Preparative Organic Chemistry; Academic Press; London, 1989; Chapter 2.

When the protecting group R_6 is benzyl, it may be removed by catalytic hydrogenation in the presence of a catalyst, such as palladium on charcoal.

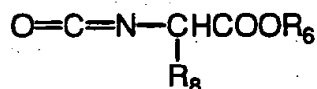
B. Reaction of a compound of the formula III

10



wherein R_1 and R_2 have the meaning given above, with a compound of the formula IV

15



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wherein R_6 has the meaning given above and R_8 is the side chain specific for an amino acid residue A as defined in claim 1, followed by removal of the protecting group R_6 , as described above, to give a compound of the formula I.

25 Preferentially the carbamoylphosphonate-forming reaction is performed at 50°C to 150°C for 1 to 50 hours.

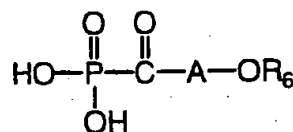
The starting materials used in the above methods of preparation A-B are known compounds, or may be prepared by known methods commonly used for the synthesis of hydroxycarbonylphosphonic acid triesters, phosphite esters, isocyanates

30

and esters of amino acids. Examples of methods for the synthesis of phosphite esters may be found in Houben-Weyl, Methoden der Organischen Chemie, Auflage 4, Band XII/2, Organische Phosphorverbindungen, p. 5-78. Examples of methods for the synthesis of hydroxycarbonylphosphonic acid triesters are found in Houben-
5 Weyl, Methoden der Organischen Chemie, Auflage 4, Band XII/1, Organische Phosphorverbindungen, p. 433-463.

C. Esterification of a compound of the formula V

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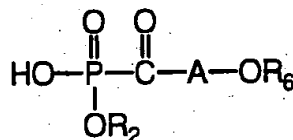
with an alcohol R_1OH , wherein A, R_1 and R_6 have the meaning given above,
15 followed by removal of the protecting group R_6 , as described above, to give a compound of the formula I where $\text{R}_1=\text{R}_2$.

The esterification reaction is performed through the intermediary of activating agents known per se for the phosphorylation of alcohols. Examples of such
20 methods are described for example by L. A. Slotin in Synthesis 1977, 737 and by H. Seliger and H. Kössel in Progress in the Chemistry of Organic Natural Products 32 (1975) 297.

Synthesis of the phosphonic acids of the formula V are described below in methods
25 J and K.

D. Esterification of a compound of the formula VI

30



5

with an alcohol R_1OH , wherein A, R_1 , R_2 and R_6 have the meaning given above, followed by removal of the protecting group R_6 , as described above, to give a compound of the formula I.

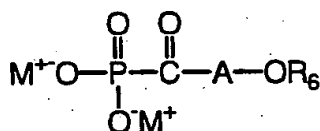
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The esterification reaction is performed through the intermediary of activating agents known per se for the phosphorylation of alcohols. Examples of such methods are described for example by L.A. Slotin in Synthesis 1977, 737 and by H. Seliger and H. Kössel in Progress in the Chemistry of Organic Natural Products 32 (1975) 297. Synthesis of the phosphonic acid monoesters of formula VI are described below in methods L-N.

15

E. Reaction of a compound of the formula VII

20



25

with a compound $\text{R}_1\text{-X}$, wherein A, R_1 and R_6 have the meaning given above, M^+ is a cation such as Ag^+ , Li^+ , Na^+ , K^+ , Cs^+ , Et_3NH^+ , $(i\text{-Pr})_2\text{NEtH}^+$ and X is a halogen such as Cl, Br or I, followed by removal of the protecting group R_6 , as described above, to give a compound of the formula I where $\text{R}_1=\text{R}_2$.

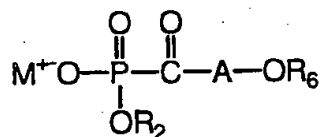
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Preferentially the esterification reaction is carried out in a solvent, such as for example ethanol or dimethylformamide, at a temperature from 25°C to 100°C for 1

to 50 hours.

F. Reaction of a compound of the formula VIII

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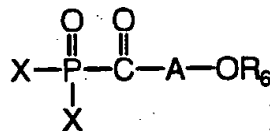


- 10 with a compound $\text{R}_1\text{-X}$, wherein A, R_1 , R_2 , R_6 , M^+ and X have the meaning given above, followed by removal of the protecting group R_6 , as described above, to give a compound of the formula I.

- 15 Preferentially the esterification reaction is carried out in a solvent, such as for example ethanol or dimethylformamide, at a temperature of 25°C to 100°C for 1 to 50 hours.

G. Reacting a compound of the formula IX

20



with an alcohol R_1OH ,

25

wherein A, R_1 , R_6 and X have the meaning given above, followed by removal of the protecting group R_6 , as described above, to give a compound of the formula I where $\text{R}_1=\text{R}_2$.

- 30 The esterification reaction is performed by methods known per se for the

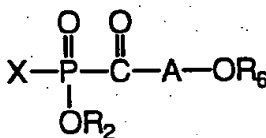
phosphorylation of alcohols by phosphoric and phosphonic acid halides. Examples of such methods are described for example by L.A. Slotin in *Synthesis* 1977, 737 and by H. Seliger and H. Kössel in *Progress in the Chemistry of Organic Natural Products* 32 (1975) 297.

5

The dihalides of the formula IX are prepared from the corresponding phosphonic acids by methods known per se for the synthesis of dihalides of phosphonic acids and phosphoric acids. References for those methods are found for example in the two publications above and in Houben-Weyl, *Methoden der Organischen Chemie*,
10 Auflage 4, Band XII/1, p. 386-406 and Band XII/2, p. 211-225 and p 274-292. The phosphonic acids are prepared by methods described in methods J and K.

H. Reacting a compound of the formula X

15

20 with an alcohol R_1OH ,

wherein A, R_1 , R_2 , R_6 and X have the meaning given above, followed by removal of the protecting group R_6 , as described above, to give a compound of the formula I.

25

The esterification reaction is performed by methods known per se for the phosphorylation of alcohols. Examples of such methods are described for example by L.A. Slotin in *Synthesis* 1977, 737 and by H. Seliger and H. Kössel in *Progress in the Chemistry of Organic Natural Products* 32 (1975) 297.

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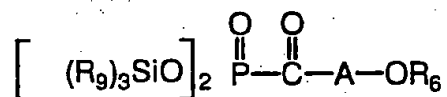
The monoester halides of the formula X are prepared from the corresponding phosphonic acid monoesters by methods known per se for the synthesis of monohalides of phosphonic and phosphoric acids. References for those methods are found for example in the two publications above and in Houben-Weyl, Methoden
 5 der Organischen Chemie, Auflage 4, Band XII/1, p. 386-406 and Band XII/2, p. 211-225 and p. 274-292.

The corresponding phosphonic acid monoesters are prepared by methods described below in L-N.

10

J. Aqueous hydrolysis of a compound of the formula XI containing two silylated phosphonate groups

15



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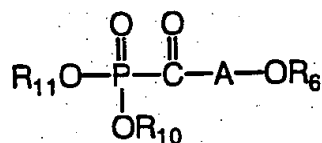
wherein A and R₆ have the meaning given above, and R₉ is an inert organic residue, for example methyl, followed by removal of the protecting group R₆, as described above, to give a compound of the formula I where R₁=R₂=H.

25

Optionally, the phosphonic acid groups formed on hydrolysing the bis-silyl esters can be neutralized. Preferably they can be neutralized with a weak cation exchanger (M⁺) or with a base such as MHCO₃, M₂CO₃ or MOH. M⁺ is NH₄⁺ or a metal cation such as Li⁺, Na⁺ or K⁺.

The phosphonate bis-silyl esters may be obtained by reacting a compound of the formula XII

30



5

with a compound $\text{X-Si}(\text{R}_9)_3$, wherein R_6 , R_9 , A and X have the meaning given above and R_{10} and R_{11} have the meaning given R_1 and R_2 . R_{10} and R_{11} may be the same or different.

10

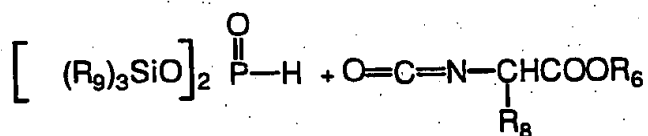
Preferentially, the reaction is performed at -20°C to reflux temperatures for 1 hour to several days.

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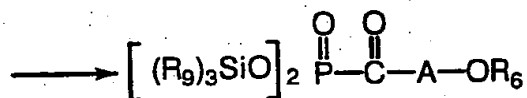
The phosphonic acid diesters of formula XII are prepared by methods analagous to those described in A-H.

Alternatively, the phosphonate bis-silyl esters may be prepared by reacting a bis-silyl phosphite with an isocyanate according to the formula

20



25

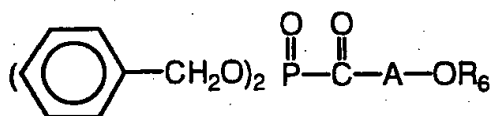


where R_6 , R_8 , R_9 and A have the meaning given above. Preferentially the reaction is performed at 25°C to 150°C for 1 to 50 hours.

30

The bis-silyl phosphites are prepared by known methods, as described for example by Sekine *et al* in J. Org. Chem. 46 (1981) 2097, for the preparation of bis(trimethylsilyl) phosphite.

5 K. Hydrogenation of a compound of the formula XIII



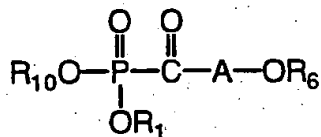
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wherein A and R₆ have the meaning given above, followed by removal of the protecting group R₆, as described above, to give a compound of the formula I where R₁=R₂=H.

15 Preferably the hydrogenation reaction may be performed with a catalyst such as palladium on charcoal. Optionally the phosphonic acid groups may be neutralized. Preferably they may be neutralized with a weak cation exchanger (M⁺) or with a base such as MHCO₃, M₂CO₃ or MOH. M⁺ is for example NH₄⁺ or a metal cation such as Li⁺, Na⁺ or K⁺.

20

L. Reacting a compound of the formula XIV



25

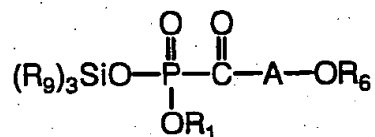
with iodide or bromide anion, wherein A, R₁, R₆ and R₁₀ have the meaning given above followed by removal of the protecting group R₆, as described above, to give
30 a compound of the formula I where R₂=H.

Preferably the reaction is carried out with sodium iodide in a solvent such as for example tetrahydrofuran or acetone. Preferably the reaction is carried out at a temperature from 20°C to 100°C from 2 hours to 7 days.

- 5 The phosphonic acid diesters of formula XIV may be prepared by methods analogous to those described in A-H.

M. Aqueous hydrolysis of a compound of the formula XV containing one silylated phosphonate group

10



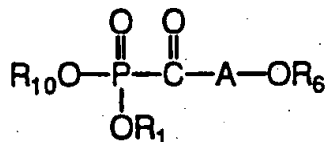
15

wherein A, R₁, R₆ and R₉ have the meaning given above, followed by removal of the protecting group R₆, as described above, to give a compound of the formula I where R₂=H.

- 20 Optionally the phosphonic acid group formed on hydrolysing the silyl ester may be neutralized. Preferably it may be neutralized with a weak cation exchanger (M⁺) or with a base such as MHCO₃, M₂CO₃ or MOH. M⁺ is for example NH₄⁺ or a metal cation such as Li⁺, Na⁺ or K⁺.

- 25 The silyl esterified phosphonate group may be obtained by reacting a compound of the formula XIV

30



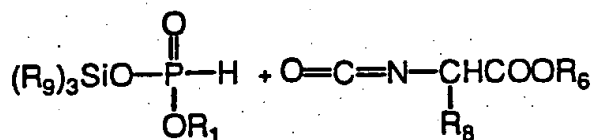
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with a compound $\text{X-Si(R}_9\text{)}_3$, wherein A, R_1 , R_6 , R_9 , R_{10} and X have the meaning given above.

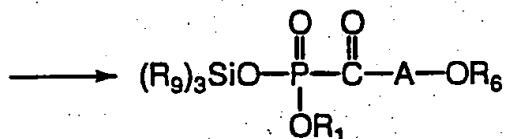
- 10 Preferably the silylation reagents are for example bromotrimethylsilane at -20°C to 50°C for 0.5 to 20 hours, or alternatively for example chlorotrimethylsilane at 20°C to reflux temperature for several days. The phosphonic acid diesters of formula XIV may be prepared by methods analogous to those described in A-H.

- 15 Alternatively, the silyl esterified phosphonate group may be prepared by reacting a silyl phosphite with an isocyanate according to the formula

20



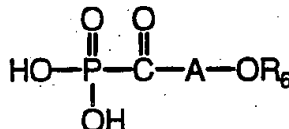
25



where R_1 , R_6 , R_8 , R_9 and A have the meaning given above. Preferentially, the reaction is carried out at 25°C to 150°C for 1 to 50 hours.

30

N. Monoesterification of a compound of the formula V



5

with an alcohol R_1OH , wherein A, R_1 and R_6 have the meaning given above, followed by removal of the protecting group R_6 , as described above, to give a compound of the formula I where $\text{R}_2=\text{H}$.

10

The esterification reaction is performed through the intermediary of activating agents known per se for the phosphorylation of alcohols. Examples of such methods are described for example by L. A. Slotin in Synthesis 1977, 737 and by H. Seliger and H. Kössel in Progress in the Chemistry of Organic Natural Products 32 (1971) 297.

15

The phosphonic acids of formula V are prepared by the methods described above in methods J and K.

20 Pharmaceutical formulations

The derivatives of PFA or salts thereof according to the invention may be used for the therapeutic and prophylactic control and treatment of herpesvirus diseases and HIV diseases. Oral formulations of the prodrugs of PFA or salts thereof can be used alone or with other antiviral agents such as acyclovir, ganciclovir, ddC, ddI, AZT or immunological agents such as interferon and growth factors such as granulocyte-macrophage and granulocyte-colony stimulating factors (GM-CSF and G-CSF).

25

30 Other drugs, which can be derivatized and used according to the present invention

are analgesics, antirheumatics and antiphlogistics, such as acemetacin, acetylsalicylic acid, alclofenac, diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacine, ketoprofen, ketozolac, naproxen, niflumic acid, oxaprozin, piroprofen, salicylic acid, sulindac, tiaprofenic acid, tolfenamic acid and tolmetin; antibacterials and antivirals such as cinoxacin, ciprofloxacin, nalidixic acid and phosphonoacetic acid; diuretics such as etacrynic acid and canrenoic acid; hemostatics such as tranexamic acid; oncolytics such as chlorambucil; prostaglandins, such as alprostadil, carboprost, dinoprost, dinoprostone and epoprostenol; and thyreomimetics such as levothyroxine and liothyronine.

10

The compounds of the present invention are suitably admixed with excipients to be formulated into capsules, tablets, suppositories and others such as suspensions and solutions. Using known pharmaceutical procedures oral formulations of capsules at doses of 50 mg to 1000 mg may be formulated.

15

For clinical use the compounds of the invention are formulated into pharmaceutical formulations for oral, preteral and rectal administration. The pharmaceutical formulation contains the compound of the invention normally in combination with a pharmaceutically acceptable excipient. The excipient may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-99% by weight of the preparation for oral as well as for other modes of administration.

20

In the preparation of pharmaceutical formulations containing the compounds of the present invention in the form of dosage units for oral administration the compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium, and the like, as

25

30

well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalyzed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

Soft gelatin capsules may be prepared with capsules containing a mixture of the active compound of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatin capsules. Soft gelatin capsules may also be enteric-coated as described above. Hard gelatin capsules may contain granules or enteric-coated granules of the active compound.

Hard gelatin capsules may also contain the active compound in combination with a powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivatives or gelatin. The hard gelatin capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories with the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatin rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatin rectal capsules, or they may be prepared in the form of a dry micro enema, or they may be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups

or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharin and carboxymethyl or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

In addition, using known pharmaceutical procedures, sustained release preparations at doses of 50 mg to 1000 mg, preferably 1000 mg may be formulated. Suitable sustained release formulations may include pharmaceutically acceptable excipients.

The typical daily dose of the active substance will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral dosages will be in the range of 50 to 20000 mg of active substance per day, preferably 200 mg to 15000 mg of active substance per day.

Experiments

Bioavailability studies

In vivo experiments were performed using male Wistar rats, breed U:WU rats. Phosphonoformic acid or a prodrug according to the present invention was administered orally or intravenously to the rat and whole blood samples (200 µl) were collected from the cannulated jugular vein and stored in heparinised cups. Oral absorption of DEPF-Gly and PFA were calculated relative to an intravenous dose of PFA in a cross-over design in 4 animals. The obtained figures of results were treated statistically to determine the standard deviation. After centrifugation, 20.0 µl plasma samples were taken and diluted with 180 µl 1 mM pyrophosphoric acid and

treated with about 20 mg activated charcoal. After intensive vortexing the samples were centrifuged for 15 min at 2000 g and the supernatant was brought into vials for a sample processor (Waters WISP 710B).

- 5 Phosphonoformic acid plasma standards (ranging from 0.5 μ M to 1 mM) prepared with rat plasma, were used to quantify the concentration of phosphonoformic acid in the samples.

10 Immediately after the workup procedure the samples were injected onto a HPLC system consisting of an LDC analytical ConstaMetric®3200 solvent delivery system with a built-in pulse dampener (Laboratory Data Control, Riviera Beach, FL, USA), a WISP 710B autosampler, a Kratos Spectroflow 773 variable wavelength UV detector operating at 230 nm, and an ESA Coulochem®II electrochemical detector (ESA Inc, Bedford, MA, USA) with a model 5011 high sensitivity
15 analytical cell. The potentials on the analytical cell were set at +0.75 and +0.95V for channels 1 and 2, resp. The mobile phase (flow rate 0.7 ml/min) was a pH 5.8 phosphate buffer-methanol (75:25, v:v) mixture with 1 mM tetrahexylammonium hydrogen sulfate as ion pair creator and 0.2 mM pyrophosphoric acid to prevent peak tailing. The total concentration of phosphate in the mobile phase was 43 mM.
20 The analytical column, a Merck LiChrospher® 100 RP 18 (5 μ m; E Merck Nederland BV, Amsterdam, NL) was held at a constant temperature of 37°C. Under these conditions phosphonoformic acid showed a retention time of 8.5 min.

25 The oral absorption of the derivative of PFA was tested compared to the oral absorption of PFA in an aqueous solution. Both oral administrations were compared to an intravenous dose of PFA to calculate the absolute bioavailability (F_{abs}). All doses were equimolar (180 μ mol/kg). Solutions for i.v. and p.a. administration were 120 mM in sterile normal saline with respect to PFA or DEPF-Gly. From Fig. 1 it can be seen that the plasma concentration after oral
30 administration of DEPF-Gly reaches a C_{max} of 0.18 mM as compared to C_{max} of

0.05 mM for PFA in aqueous solution. The bioavailability measured as F_{abs} is 0.64 for DEPF-Gly as compared to 0.19 for PFA in aqueous solution which corresponds to an over 3-fold increase. The time to reach C_{max} was 1.5 h for DEPF-Gly and 1.25 h for PFA. For a compilation of results see Table 1.

5

Table 1

	Dose		AUC	F_{abs}
	<u>Compound</u>	<u>(μmol/kg)</u> <u>Route</u>	<u>(mM•h)</u>	
	PFA	180 i.v.	0.58 ± 0.05	-
10	PFA	180 p.o.	0.10 ± 0.02	0.19 ± 0.04
	DEPF-Gly	180 p.o.	0.37 ± 0.05	0.64 ± 0.12

In vitro intestinal transport study

- 15 Transport of DEPF-Gly across living intestinal tissue was performed in Ussing chambers (Ussing, H.H. and Zehran, K., Acta Physiol. Scand. 23:110-127(1951)) in the following way: Rat intestine (Wistar rats, breed U:WU) was stripped of its underlying muscle layer, placed between two Lucite® chambers and bathed on both sides with a TRIS-Ringer solution with a pH of 7.4 containing 10 mM
- 20 glucose at the serosal side and 10 mM mannitol on the mucosal side. During transport studies tissue integrity was monitored using fluorescein as a fluorescent transport marker. The viability was monitored measuring potential difference and short-circuited current of the tissue.
- 25 After equilibration during 45 min, PFA or DEPF-Gly was added to the donor side of the membrane at a concentration of 1 mM. For studies of the transport from the mucosal to the serosal side (m-to-s) the substance to be tested was added on the mucosal side and for transport in the opposite direction (s-to-m) it was added on the serosal side. At intervals of 30 min samples were taken from the acceptor phase
- 30 up to 210 minutes. In order to maintain a constant volume, TRIS-Ringer solution

with 10 mM glucose for the mucosal to serosal side studies and Tris-Ringer solution with 10 mM mannitol for the serosal to mucosal side studies was added. The acceptor samples were assayed for PFA or DEPF-Gly using the HPLC assay described above.

5

Fig. 2 illustrates the transport of PFA and DEPF-Gly at a donor concentration of 1 mM during a period of 210 minutes over rat jejunum. A higher m-to-s (closed symbols) transport rate than s-to-m (open symbols) transport rate was observed. This suggests that in transport from the mucosal to serosal side another mechanism

10

Example 1

Di-(O-ethyl)phosphonoformylglycine was prepared in two steps in the following way:

15

Step 1

Preparation of di-(O-ethyl)phosphonoformylglycine-ethyl ester (DEPF-Gly-OEt; M_w 267).

20

Dioxane was refluxed overnight over cuprous chloride (CuCl) and freshly distilled before use. 6.3 ml (47.9 mmol; 1.2 eq) trimethylsilyl azide (TMSA) was slowly added to 50 ml dioxane under an argon atmosphere. 5 ml (39.7 mmol; 1 eq) ethyl malonyl chloride (EMC) was slowly added to this mixture under continuous stirring. After 15 minutes the temperature was raised to 90-100°C. Vigorous stirring of the yellow solution resulted in the escape of nitrogen bubbles, which stopped after 3 hours. Trimethylsilyl chloride (TMSC; b.p. 56-57°C) formed during the reaction distilled off. Then 6.2 ml (48.1 mmol; 1.2 eq) diethylphosphite (DEP)

30

was added dropwise to the resulting reaction mixture and was refluxed for 1.5 hrs.

Dioxane was removed under reduced pressure to give a thick yellow liquid (78% yield).

A sample was further purified by extraction from DCM to give a pale yellow liquid.

- 5 Bp 172°C;
 $n=1.398$;
 $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) $\delta(\text{ppm})$ 1.1 (t, 6H), 1.3 (t, 3H), 4.45 (m, 6H), 3.6 (m, 2H); EI-MS; 267 (M/Z);
 FAB-MS: 268 (M+1);
10 FT-IR (cm^{-1}): 3271 (m, NH), 3000 (s, CH_2/CH_3), 1752 (s, C=O aliphatic ester), 1662 (s, NHCO), 1520 (m, NHCO), 1250 (s, P=O), 1200 (s, P-O), 875 (s, CH_2/CH_3).

Step 2

15

Preparation of di-(O-ethyl)phosphonoformylglycine(DEPF-Gly; M_w 239).

- 0.782 g DEPF-GlyOEt was dissolved in 1 ml water. This mixture was poured into 2.0 ml 0.1M borate-buffer (pH 8) and 70 μl (200 units) porcine liver esterase (PLE;
20 carboxylic ester hydrolase; EC 3.1.1.1) was added conforming with Sigma PLE product information. This mixture was stirred overnight keeping the pH at 8 by adding 0.1M NaOH-solution. The reaction was stopped by adding 5.0 ml dichloromethane (DCM) to the mixture which denaturated the esterase. After filtration of the brown precipitate the aqueous layer was extracted three times with
25 DCM. The aqueous layer was neutralised and further purified by silica gel chromatography which yielded 62% of compound DEPF-Gly as a white solid.

- UV: $\lambda_{\text{max}}=208.3$ nm;
 Mp 160-162°C;
 $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) $\delta(\text{ppm})$ 1.2 (t, 6H), 4.1 (d, 4H), 3.85 (d,
30 2H), 8.7 (s, 1H);

FAB-MS: 240 (M+1);

FT-IR (cm^{-1}): 3520 (w, OH), 3271 (m, NH), 3000 (s, CH_2/CH_3), 1662 (s, NHCO), 1520 (m, NHCO), 1250 (s, P=O), 1200 (s, P-O), 875 (s, CH_2/CH_3).

5

The following examples illustrate the preparation of pharmaceutical compositions of the invention. The active substance is preferably used in the form of a solid salt where such salts can be formed and most preferably in the form of its sodium salt.

10

Example 2

Tablets

15

Each tablet contains:

20

active substance	300.0 mg
lactose	200.0 mg
maize starch	25.0 mg
gelatin	1.5 mg
talc	12.0 mg
magnesium stearate	1.5 mg

Example 3

Coated tablets

- 5 Tablets according example 2 are coated with an enteric coating solution with the following composition:

	ethyl cellulose	120.0 g
	propylene glycol	30.0 g
10	sorbitan monooleate	10.0 g
	water	ad 1000.0 ml

The coating is carried out by a pouring procedure in a conventional coating pan or by spraying the tablets in a pan spray tablet coater.

15

Example 4

Gastric juice-resistant tablets

- 20 Tablets according example 2 are coated with a coating solution with the following composition:

	cellulose acetate phthalate	120.0 g
	propylene glycol	30.0 g
25	sorbitan monooleate	10.0 g
	ethanol 95%	450.0 ml
	acetone	q.s. ad 1000.0 ml

- 30 The coating is carried out by a pouring procedure in a conventional coating pan or by spraying the tablets in a pan spray tablet coater.

Example 5

Syrup

5	active substance	12.0 g
	liquid glucose	30.0 g
	sucrose	40.0 g
	ascorbic acid	0.1 g
	disodium edetate	10.0 mg
10	lemon essence	25.0 mg
	purified water	ad 100.0 g

Example 6

15 Powder for suspension (Sachet)

Each sachet contains:

	active substance	3.0 g
20	citric acid anhydrous	0.5 g
	glucose	2.5 g

Example 7

Capsules

5 Each capsule contains:

active substance	300.0 mg
microcrystalline cellulose	150.0 mg
colloidal silicium oxide	5.0 mg

10

Example 8

Solution for injection

15	active substance	5.0 g
	disodium edetate	2.5 mg
	sodium chloride for isotonia	q.s.
	hydrochloric acid to pH 6.5-7	
	sterile water for injection	ad 100.0 ml

20

Example 9

Suppositories

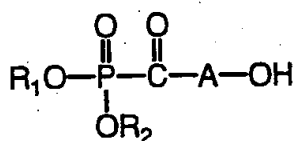
25 Each suppository contains:

active substance	500.0 mg
adeps solidus	q.s.

Claims

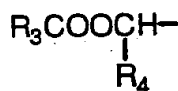
1. A compound of the formula I

5



- 10 wherein R_1 and R_2 each independently are hydrogen; a branched or unbranched C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl or C_{1-6} -alkoxy- C_{1-6} -alkyl group which is optionally substituted with hydroxy, amino, halogen or oxo; a benzyl group;

a group

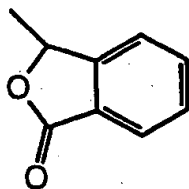


or a group

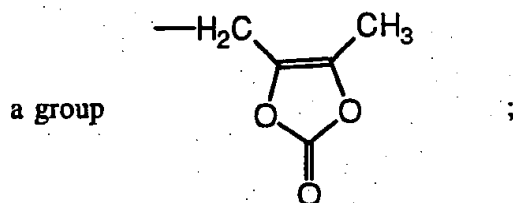


- 15 wherein R_3 is a branched or unbranched C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl or C_{1-6} -alkoxy- C_{1-6} -alkyl group which is optionally substituted with hydroxy, amino, halogen or oxo; and R_4 is hydrogen or a C_{1-4} -alkyl group;

a group

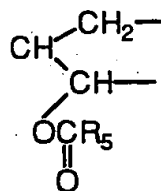


;



or wherein R_1 and R_2 together form a group

5



wherein R_5 is a branched or unbranched C_{1-6} -alkyl or C_{1-6} -alkoxy group;

10

A is an amino acid residue which is selected from glycyl, alanyl, valyl, norvalyl, leucyl, isoleucyl, norleucyl, phenylalanyl, tyrosyl, seryl, homoseryl, threonyl, cysteinyl, methionyl, tryptophyl, α -aspartyl, α -glutamyl, arginyl, lysyl, histidyl, ornithyl, prolyl or 4-hydroxyprolyl either in the L- or in the D-configuration; or

15 physiologically acceptable salts thereof.

2. A compound according to claim 1 wherein A is a glycyl residue.

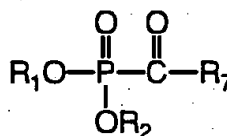
3. A compound according to claim 1 wherein A is a L-alanyl residue.

20

4. A compound according to claim 1 wherein A is a L-phenylalanyl residue.

5. A compound according to claim 1 wherein A is a L-prolyl residue.

6. A compound according to claim 1 wherein A is a L-4-hydroxypropyl residue.
7. A compound according to claim 1 wherein A is a L-tyrosyl residue.
- 5 8. A compound according to claim 1 wherein R_1 and R_2 are ethyl.
9. A process for the preparation of a compound of the formula I as defined in claim 1, characterized by
- 10 A. reaction of a compound of the formula II

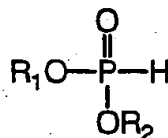


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wherein R_1 and R_2 have the meaning given above and R_7 is an aliphatic cycloaliphatic, araliphatic, aromatic or heterocyclic leaving group, such as C_{1-6} -alkoxy, C_{3-8} -cycloalkoxy, benzyloxy, phenoxy, 4-nitrophenoxy, imidazolyl or

20 succinimidoxy with an amino acid derivative H-A-OR_6 , wherein A has the meaning given above and R_6 is a suitable protecting group such as methyl, ethyl or benzyl, followed by removal of the protecting group R_6 to give a compound of the formula I, or

- 25 B. reaction of a compound of the formula III



30

wherein R_1 and R_2 have the meaning given above, with a compound of the formula IV



wherein R_6 has the meaning given above and R_8 is the side chain specific for an amino acid residue A as defined in claim 1, followed by removal of the protecting group R_6 to give a compound of the formula I, or

10

C. esterification of a compound of the formula V



with an alcohol $R_1\text{OH}$, wherein A, R_1 and R_6 have the meaning given above, followed by removal of the protecting group R_6 to give a compound of the formula I where $R_1=R_2$, or

20

D. esterification of a compound of the formula VI



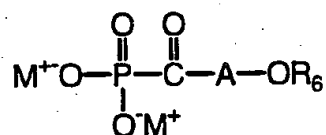
with an alcohol $R_1\text{OH}$, wherein A, R_1 , R_2 and R_6 have the meaning given above, followed by removal of the protecting group R_6 to give a compound of the formula

30

I, or

E. reaction of a compound of the formula VII

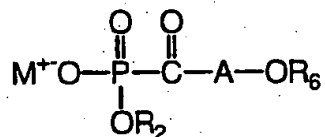
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10 with a compound $\text{R}_1\text{-X}$, wherein A, R_1 and R_6 have the meaning given above, M^+ is a cation such as Ag^+ , Li^+ , Na^+ , K^+ , Cs^+ , Et_3NH^+ , $(i\text{-Pr})_2\text{NEtH}^+$ and X is a halogen such as Cl, Br or I, followed by removal of the protecting group R_6 to give a compound of the formula I where $\text{R}_1=\text{R}_2$, or

F. reaction of a compound of the formula VIII

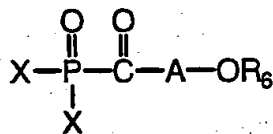
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with a compound $\text{R}_1\text{-X}$, wherein A, R_1 , R_2 , R_6 , M^+ and X have the meaning given above, followed by removal of the protecting group R_6 to give a compound of the formula I, or

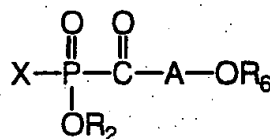
25 G. reacting a compound of the formula IX



30

with an alcohol R_1OH , wherein A, R_1 , R_6 and X have the meaning given above, followed by removal of the protecting group R_6 to give a compound of the formula I where $R_1=R_2$, or

5 H. reacting a compound of the formula X



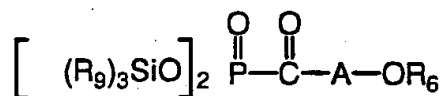
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with an alcohol R_1OH , wherein A, R_1 , R_2 , R_6 and X have the meaning given above, followed by removal of the protecting group R_6 to give a compound of the formula I, or

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J. aqueous hydrolysis of a compound of the formula XI containing two silylated phosphonate groups

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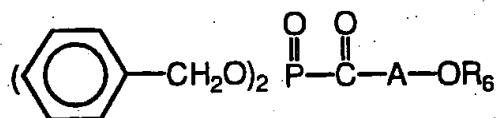


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wherein A and R_6 have the meaning given above, and R_9 is an inert organic residue, for example methyl, followed by removal of the protecting group R_6 to give a compound of the formula I where $R_1=R_2=H$, or

K. hydrogenation of a compound of the formula XIII

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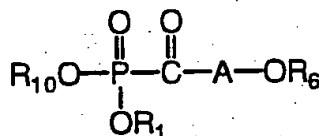


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wherein A and R₆ have the meaning given above, followed by removal of the protecting group R₆ to give a compound of the formula I where R₁=R₂=H, or

L. reacting a compound of the formula XIV

10

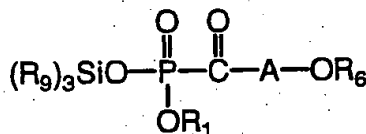


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with iodide or bromide anion, wherein A, R₁ and R₆ have the meaning given above, and R₁₀ has the meaning given R₁ and R₂, followed by removal of the protecting group R₆ to give a compound of the formula I where R₂=H, or

20

M. aqueous hydrolysis of a compound of the formula XV containing one silylated phosphonate group

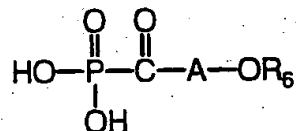


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wherein A, R₁, R₆ and R₉ have the meaning given above, followed by removal of the protecting group R₆ to give a compound of the formula I where R₂=H, or

30

N. monoesterification of a compound of the formula V

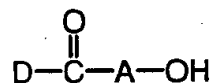


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with an alcohol R_1OH , wherein A, R_1 and R_6 have the meaning given above, followed by removal of the protecting group R_6 to give a compound of the formula I where $\text{R}_2=\text{H}$.

10

10. A compound according to the formula



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wherein $\begin{array}{c} \text{O} \\ \parallel \\ \text{D}-\text{C} \end{array}$ is a radical of a drug $\text{D}-\text{COOH}$, which is not an α -amino

acid or a peptide, and which is able to form an amide bond with an amino acid, and

20 A is defined as in claim 1.

11. A compound according to any of claims 1 to 8 or 10 for use in therapy.

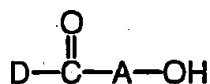
12. A compound according to any of claims 1 to 8 for use in the treatment of viral
25 infections.

12. A compound according to any of claims 1 to 8 for use in the treatment of herpesvirus infections.
13. A compound according to any of claims 1 to 8 for use in the treatment of HIV
5 infections including the state of AIDS.
14. A compound according to claim 10, wherein D-COOH is an antibacterial drug for use in the treatment of bacterial infections.
- 10 15. A compound according to claim 10 wherein D-COOH is an analgesic drug for use in the treatment of pain.
16. A compound according to claim 10 wherein D-COOH is an antirheumatic drug for use in the treatment of arthritis.
- 15 17. A compound according to claim 10, wherein D-COOH is an antiphlogistic drug for use in the treatment of inflammatory diseases.
18. A compound according to claim 10, wherein D-COOH is an oncolytic drug for
20 use in the treatment of tumors.
19. A compound according to claim 10, wherein D-COOH is a drug of the prostaglandin group for use in the control of acid secretion in the stomach.
- 25 20. A compound according to claim 10, wherein D-COOH is a drug of the prostaglandin group for use in the control of smooth muscle contractions in the uterus.
21. A compound according to claim 10, wherein D-COOH is a diuretic drug for
30 use in increasing diuresis.

22. The use of a compound according to any of claims 1 to 8 in the manufacture of a formulation for the treatment of viral infections.
23. The use of a compound according to any of claims 1 to 8 in the manufacture of
5 a formulation for the treatment of herpesvirus infections.
24. The use of a compound according to any of claims 1 to 8 in the manufacture of a formulation for the treatment of HIV including the state of AIDS.
- 10 25. The use of a compound according claim 10, wherein D-COOH is an antibacterial drug in the manufacture of a formulation for the treatment of bacterial infections.
26. The use of a compound according to claim 10, wherein D-COOH is an
15 analgesic drug in the manufacture of a formulation for the treatment of pain.
27. The use of a compound according to claim 10, wherein D-COOH is an antirheumatic drug in the manufacture of a formulation for the treatment of
20 arthritis.
28. The use of a compound according to claim 10, wherein D-COOH is an antiphlogistic drug in the manufacture of a formulation for the treatment of inflammatory diseases.
- 25 29. The use of a compound according claim 10, wherein D-COOH is an oncolytic drug in the manufacture of a formulation for the treatment of tumors.
30. The use of a compound according to claim 10, wherein D-COOH is a drug of the prostaglandin group in the manufacture of a formulation for the control of acid
30 secretion in the stomach.

31. The use of a compound according to claim 10, wherein D-COOH is a drug of the prostaglandin group in the manufacture of a formulation for the control of smooth muscle contraction in the uterus.
- 5 32. The use of a compound according to claim 10, wherein D-COOH is a diuretic drug in the manufacture of a formulation for the increasing diuresis.
33. A method for the treatment of herpesvirus infection wherein a therapeutically active amount of a compound according to any of claims 1 to 8 is administered to
10 a mammal in the need of such treatment.
34. A method for the treatment of HIV infections including AIDS wherein a therapeutically active amount of a compound according to any of claims 1 to 8 is administered to a mammal in the need of such treatment.
- 15 35. A method for the treatment of bacterial infections wherein a therapeutically active amount of a compound according to claim 10, wherein D-COOH is an antibacterial drug is administered to a mammal in the need of such.
- 20 36. A method for the treatment of pain wherein a therapeutically active amount of a compound according to claims 10, wherein D-COOH is an analgesic drug is administered to a mammal in the need of such treatment.
38. A method for the treatment of arthritis wherein a therapeutically active amount
25 of a compound according to claim 10, wherein D-COOH is an antirheumatic drug is administered to a mammal in the need of such treatment.
39. A method for the treatment of inflammatory diseases wherein a therapeutically active amount of a compound according to claim 10, wherein D-COOH is an
30 antiphlogistic drug is administered to a mammal in the need of such treatment.

40. A method for the treatment of tumors wherein a therapeutically active amount of a compound according to claim 10, wherein D-COOH is an oncolytic drug is administered to a mammal in the need of such treatment.
- 5 41. A method for the control of acid secretion in the stomach wherein a therapeutically active amount of a compound according to claim 10, wherein D-COOH is a drug of the prostaglandin group is administered to a mammal in the need of such treatment.
- 10 42. A method for the control of contractions in the uterus wherein a therapeutically active amount of a compound according to claim 10, wherein D-COOH is a drug of the prostaglandin group is administered to a mammal in the need of such treatment.
- 15 43. A method for increasing diuresis wherein a therapeutically active amount of a compound according to claim 10, wherein D-COOH is a diuretic drug is administered to a mammal in the need of such treatment.
- 20 44. The use of an amino acid moiety A-OH in the preparation of prodrugs of the general formula

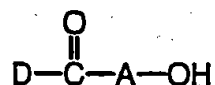


- 25 wherein A is defined as in claim 1, and

wherein $\text{D}-\overset{\text{O}}{\parallel}{\text{C}}$ is defined as in claim 10,

for increasing the uptake via the gastrointestinal tract into the blood of the parent drug D-COOH.

45. The use of an amino acid as agent to be linked by an amide bond to form a
5 compound of the general formula



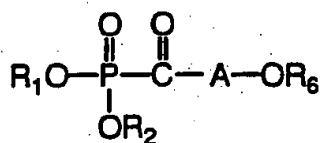
- 10 wherein A is defined as in claim 1, and

wherein $\text{D}-\overset{\text{O}}{\parallel}{\text{C}}$ is defined as in claim 10

for increasing the uptake via the gastrointestinal into the blood of the parent drug D-COOH.

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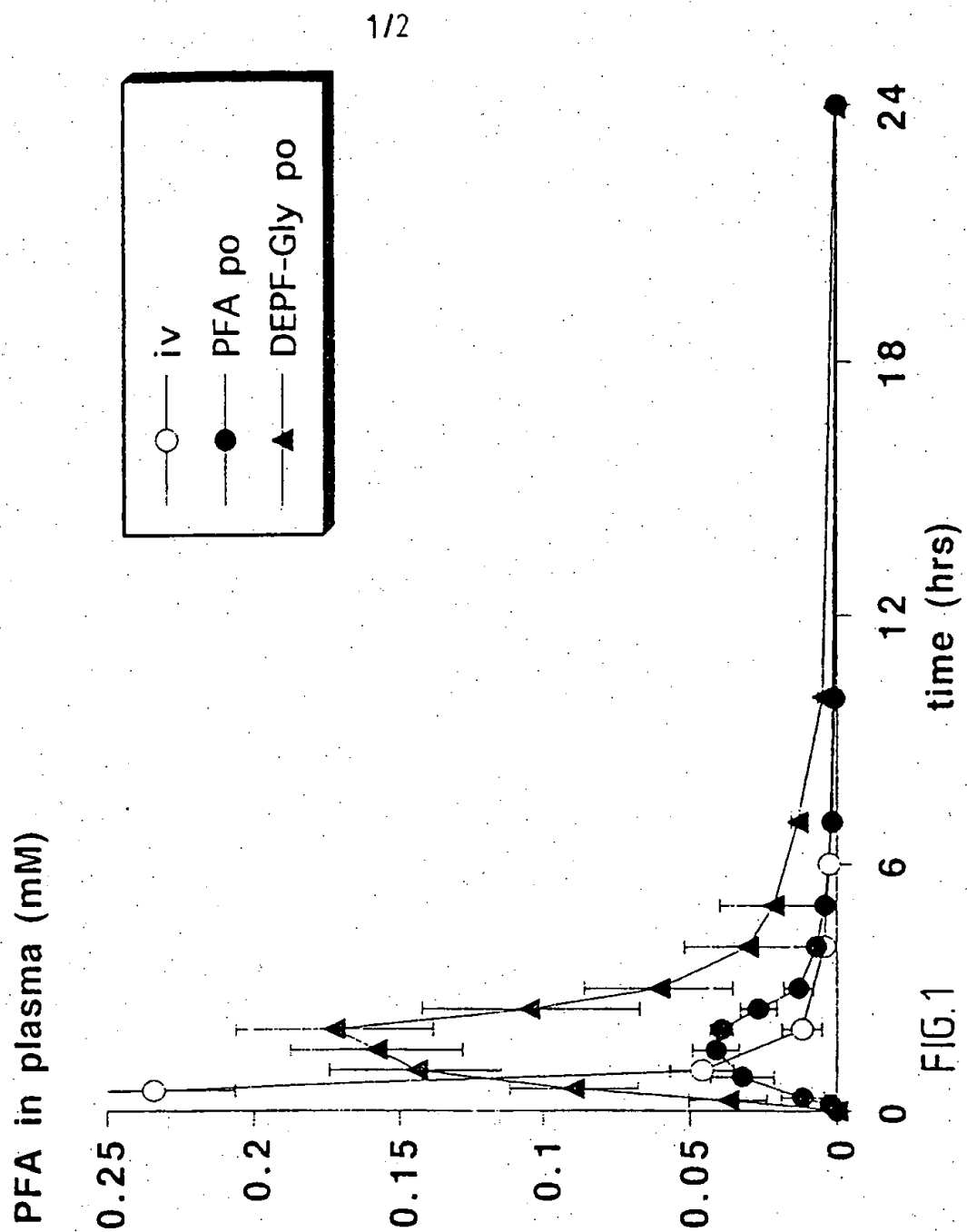
46. A compound of the formula

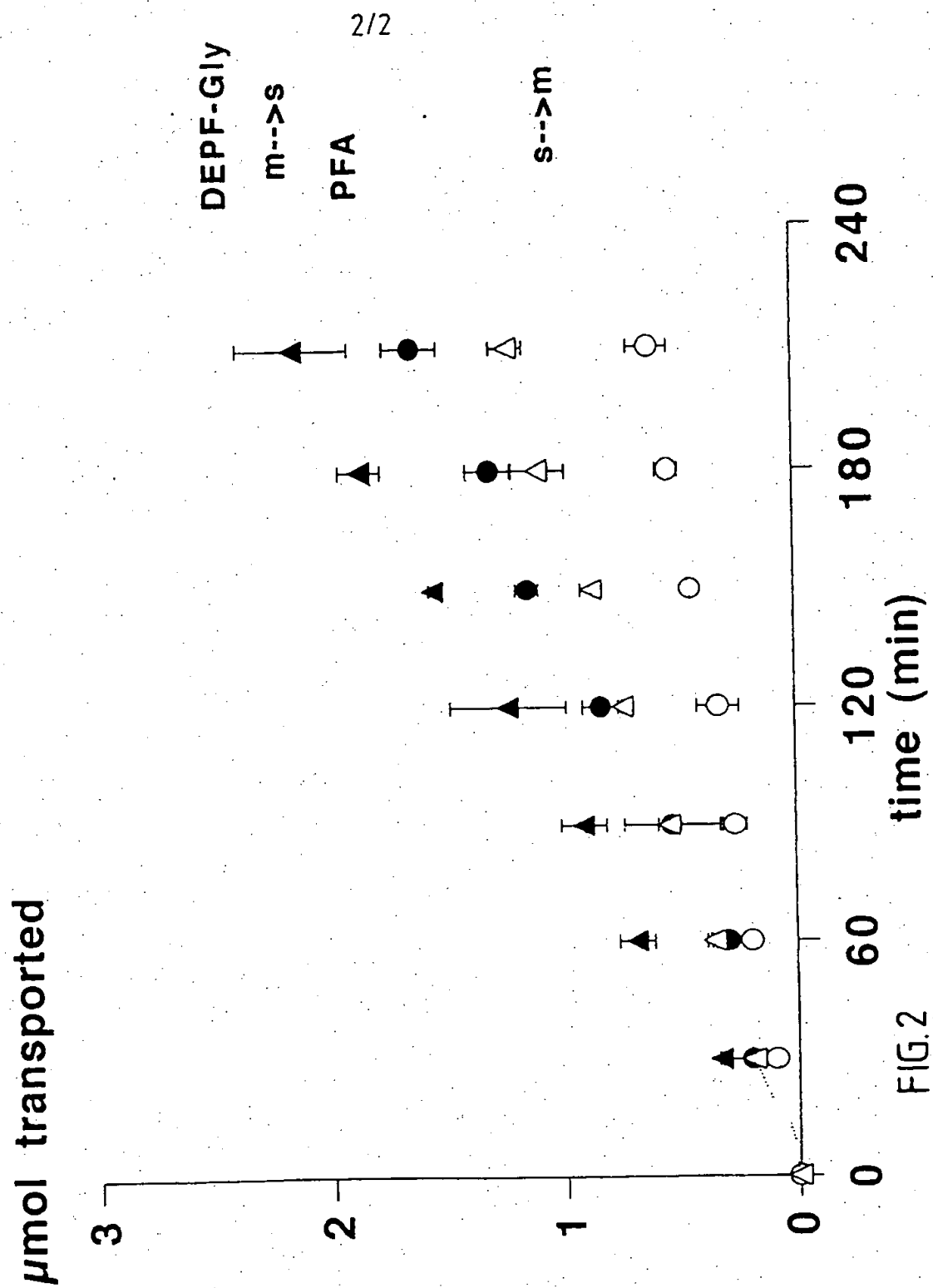


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wherein R_1 , R_2 , R_6 and A have the meaning given in claims 1 and 9.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00998

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: C07F 9/38, C07F 9/40, A61K 31/66
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DD, A1, 242811 (MARTIN-LUTHER-UNIVERSITÄT HALLE WITTENBERG), 11 February 1987 (11.02.87)	1-9,11-13, 22-24,46
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A	US, A, 4357329 (GERHARD HEYWANG ET AL), 2 November 1982 (02.11.82), see compound 14	1
	--	
A	EP, A1, 0003008 (ASTRA LÄKEMEDEL AKTIEBOLAG), 11 July 1979 (11.07.79)	1-9,11-13, 22-24,46
	-- -----	

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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| <ul style="list-style-type: none"> * Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed | <ul style="list-style-type: none"> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family |
|---|--|

Date of the actual completion of the international search	Date of mailing of the international search report
31 May 1994	13-06-1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT
Information on patent family members

07/05/94

International application No.
PCT/SE 93/00998

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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US-A-	4357329	02/11/82	AT-E,T-	4504	15/09/83
			AU-B-	537951	19/07/84
			AU-A-	7249281	14/01/82
			CA-A-	1167857	22/05/84
			DE-A-	3026326	11/02/82
			EP-A,B-	0043978	20/01/82
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